

In the Claims

Please amend the claims as shown below:

1. (amended) A conjugate which is useful for the treatment of prostate cancer which comprises a cytotoxic agent attached to an oligopeptide, wherein the oligopeptide comprises a sequence of amino acids that is selectively proteolytically cleaved by free prostate specific antigen and wherein the means of attachment is through a hydroxyalkyl-amino chemical linker which is optionally substituted,

and wherein the cytotoxic agent is a vinca alkaloid cytotoxic agent;

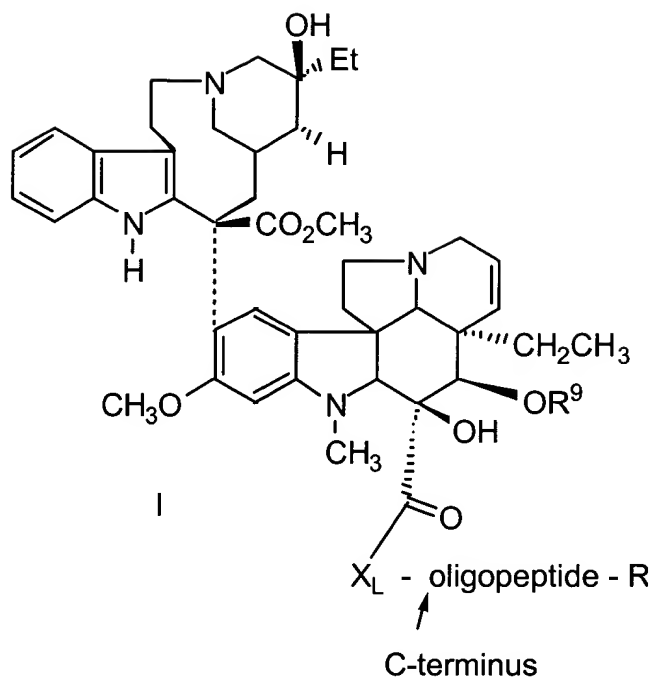
or the pharmaceutically acceptable salt thereof.

2. (original) The conjugate according to Claim 1 wherein the oligopeptide is attached to the chemical linker by an ester bond with that bond comprising the hydroxyl moiety of the chemical linker.

3. cancelled

4. (amended) The conjugate according to Claim 1 ~~3~~ wherein the cytotoxic agent is selected from vinblastine and 4-desacetylvinblastine.

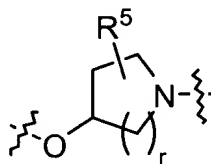
5. (original) A conjugate of the formula I:



wherein:

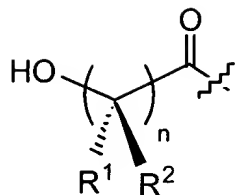
oligopeptide is an oligopeptide which is specifically recognized by the free prostate specific antigen (PSA) and is capable of being proteolytically cleaved by the enzymatic activity of the free prostate specific antigen,

X<sub>L</sub> is selected from -NH-(CR<sup>3</sup><sub>2</sub>)<sub>u</sub>(CR<sup>4</sup><sub>2</sub>)<sub>v</sub>-O- and

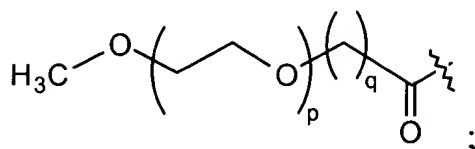


R is selected from

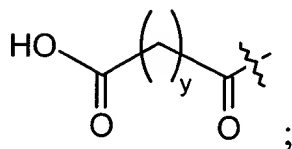
- a) hydrogen,
- b) -(C=O)R<sup>1a</sup>,
- c)



d)



e)



- f) ethoxysquarate; and  
g) cotininyll;

R<sup>1</sup> and R<sup>2</sup> are independently selected from:

- hydrogen,
- unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, R<sup>6</sup>O-, R<sup>6</sup>C(O)NR<sup>6</sup>-, (R<sup>6</sup>)<sub>2</sub>NC(O)-, R<sup>6</sup><sub>2</sub>N-C(NR<sup>6</sup>)-, R<sup>7</sup>S(O)<sub>2</sub>NH, CN, NO<sub>2</sub>, R<sup>6</sup>C(O)-, N<sub>3</sub>, -N(R<sup>6</sup>)<sub>2</sub>, or R<sup>7</sup>OC(O)NR<sup>6</sup>-,
- unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl,
- substituted C<sub>1</sub>-C<sub>6</sub> alkyl wherein the substituent on the substituted C<sub>1</sub>-C<sub>6</sub> alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, R<sup>6</sup>O-, R<sup>7</sup>S(O)<sub>2</sub>NH, R<sup>6</sup>C(O)NR<sup>6</sup>-, (R<sup>6</sup>)<sub>2</sub>NC(O)-, R<sup>6</sup><sub>2</sub>N-C(NR<sup>6</sup>)-, CN, R<sup>6</sup>C(O)-, N<sub>3</sub>, -N(R<sup>6</sup>)<sub>2</sub>, and R<sup>7</sup>OC(O)-NR<sup>6</sup>-; or

R<sup>1</sup> and R<sup>2</sup> are combined to form  $-(CH_2)_s-$  wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)<sub>m</sub>, -NC(O)-, NH and -N(COR<sup>7</sup>)- ;

R<sup>1a</sup> is C<sub>1</sub>-C<sub>6</sub>-alkyl, hydroxylated C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, polyhydroxylated C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, hydroxylated aryl, polyhydroxylated aryl or aryl,

R<sup>3</sup> and R<sup>4</sup> are independently selected from: hydrogen, C<sub>1</sub>-C<sub>6</sub>-alkyl, hydroxylated C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, polyhydroxylated C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, hydroxylated aryl, polyhydroxylated aryl and aryl, or

one R<sup>3</sup> and one R<sup>4</sup> are combined to form a  $-(CH_2)_w-$ , which is unsubstituted or substituted with one or two substituents selected from OH and C<sub>1</sub>-C<sub>6</sub> alkyl; or

an R<sup>3</sup> is combined with another R<sup>3</sup> on the same carbon to form a  $-(CH_2)_x-$ ; or

an R<sup>4</sup> is combined with another R<sup>4</sup> on the same carbon to form a  $-(CH_2)_x-$ ;

R<sup>5</sup> is selected from OH and C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>6</sup> is selected from: hydrogen, aryl, substituted aryl, heterocycle, substituted heterocycle, C<sub>1</sub>-C<sub>6</sub> alkyl and C<sub>3</sub>-C<sub>10</sub> cycloalkyl;

R<sup>7</sup> is selected from: aryl, substituted aryl, heterocycle, substituted heterocycle, C<sub>1</sub>-C<sub>6</sub> alkyl and C<sub>3</sub>-C<sub>10</sub> cycloalkyl;

R<sup>9</sup> is hydrogen, (C<sub>1</sub>-C<sub>3</sub> alkyl)-CO, or chlorosubstituted (C<sub>1</sub>-C<sub>3</sub> alkyl)-CO;

n is 1, 2, 3 or 4;

p is zero or an integer between 1 and 100;

q is 0 or 1, provided that if p is zero, q is 1;  
r is 1, 2 or 3;  
s is 4, 5 or 6;  
t is 3 or 4;  
u and v are independently selected from: 0, 1, 2 or 3;  
w is 2, 3 or 4;  
x is 3, 4 or 5;  
y is 1, 2 or 3;

or a pharmaceutically acceptable salt thereof.

6. (original) The conjugate according to Claim 5 wherein:  
oligopeptide is an oligomer that comprises an amino acid sequence selected from:

- a) AsnLysIleSerTyrGln|Ser (SEQ.ID.NO.: 1),
- b) LysIleSerTyrGln|Ser (SEQ.ID.NO.: 2),
- c) AsnLysIleSerTyrTyr|Ser (SEQ.ID.NO.: 3),
- d) AsnLysAlaSerTyrGln|Ser (SEQ.ID.NO.: 4),
- e) SerTyrGln|SerSer (SEQ.ID.NO.: 5);
- f) LysTyrGln|SerSer (SEQ.ID.NO.: 6);
- g) hArgTyrGln|SerSer (SEQ.ID.NO.: 7);
- h) hArgChaGln|SerSer (SEQ.ID.NO.: 8);
- i) TyrGln|SerSer (SEQ.ID.NO.: 9);
- j) TyrGln|SerLeu (SEQ.ID.NO.: 10);

- k) TyrGln|SerNle (SEQ.ID.NO.: 11);
- l) ChgGln|SerLeu (SEQ.ID.NO.: 12);
- m) ChgGln|SerNle (SEQ.ID.NO.: 13);
- n) SerTyrGln|Ser (SEQ.ID.NO.: 14);
- o) SerChgGln|Ser (SEQ.ID.NO.: 15);
- p) SerTyrGln|SerVal (SEQ.ID.NO.: 16);
- q) SerChgGln|SerVal (SEQ.ID.NO.: 17);
- r) SerTyrGln|SerLeu (SEQ.ID.NO.: 18);
- s) SerChgGln|SerLeu (SEQ.ID.NO.: 19);
- t) HaaXaaSerTyrGln|Ser (SEQ.ID.NO.: 20);
- u) HaaXaaLysTyrGln|Ser (SEQ.ID.NO.: 21);
- v) HaaXaaHArgTyrGln|Ser (SEQ.ID.NO.: 22);
- w) HaaXaaHArgChaGln|Ser (SEQ.ID.NO.: 23);
- x) HaaTyrGln|Ser (SEQ.ID.NO.: 24);
- y) HaaXaaSerChgGln|Ser (SEQ.ID.NO.: 25);
- z) HaaChgGln|Ser (SEQ.ID.NO.: 26);

- aa) SerChgGln|SerSer (SEQ.ID.NO.: 106);
- bb) SerChgGln|SerPro (SEQ.ID.NO.: 107); and
- cc) SerChgGln|SerAbu (SEQ.ID.NO.: 108);

wherein Haa is a cyclic amino acid substituted with a hydrophilic moiety, hArg is homoarginine, Xaa is any amino acid, Cha is cyclohexylalanine, Abu is 2-aminobutyric acid and Chg is cyclohexylglycine;

or an optical isomer thereof.

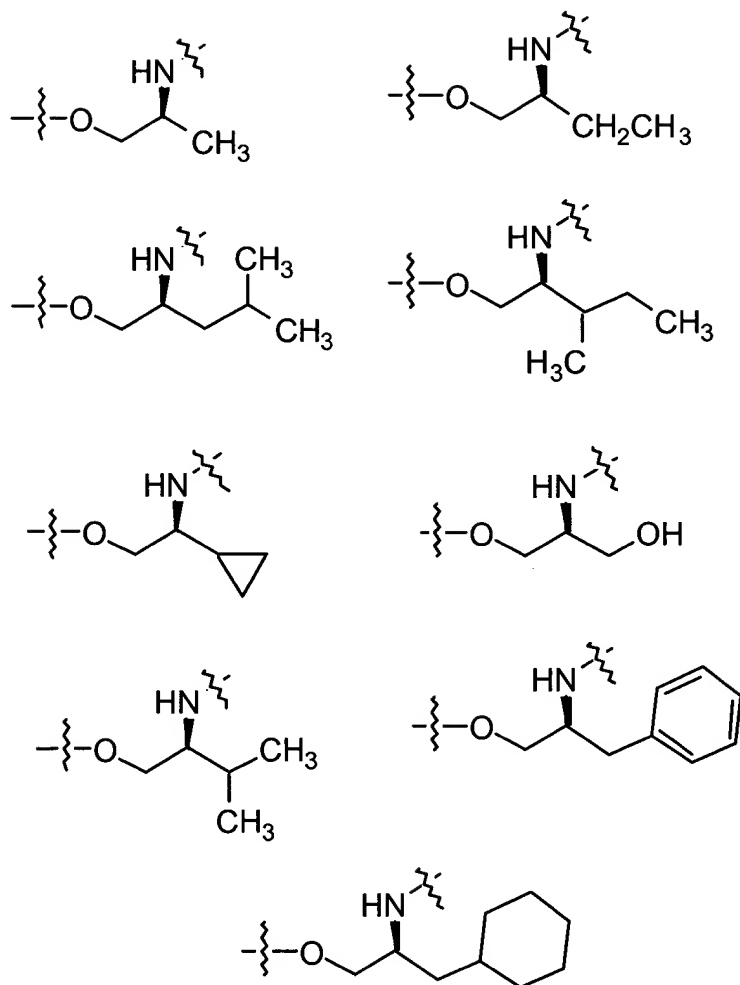
7. (original) The conjugate according to Claim 6 wherein:

Xaa is alanine, serine or isoleucine; and  
Haa is *trans*-4-hydroxy-L-proline;

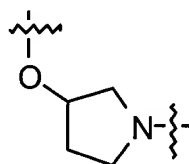
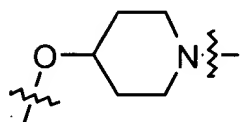
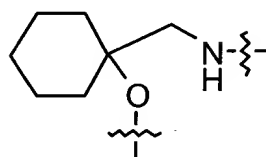
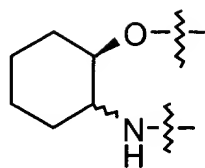
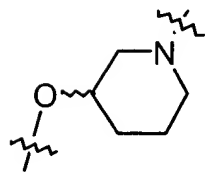
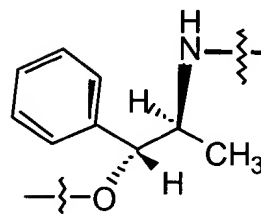
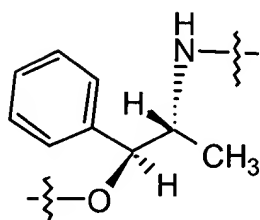
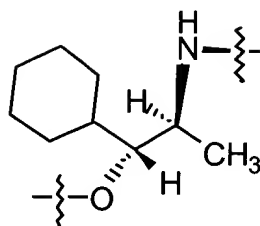
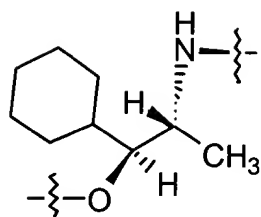
or an optical isomer thereof.

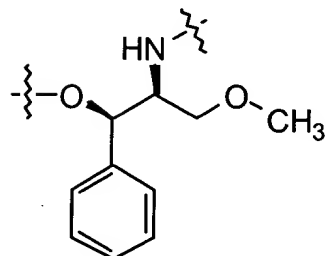
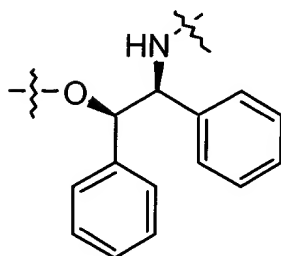
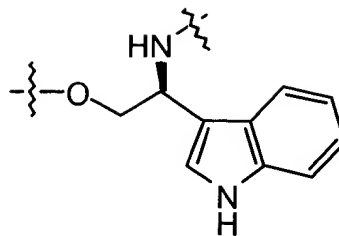
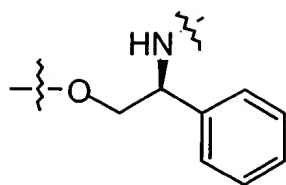
8. (original) The conjugate according to Claim 5 wherein:

X<sub>L</sub> is selected from the following group:









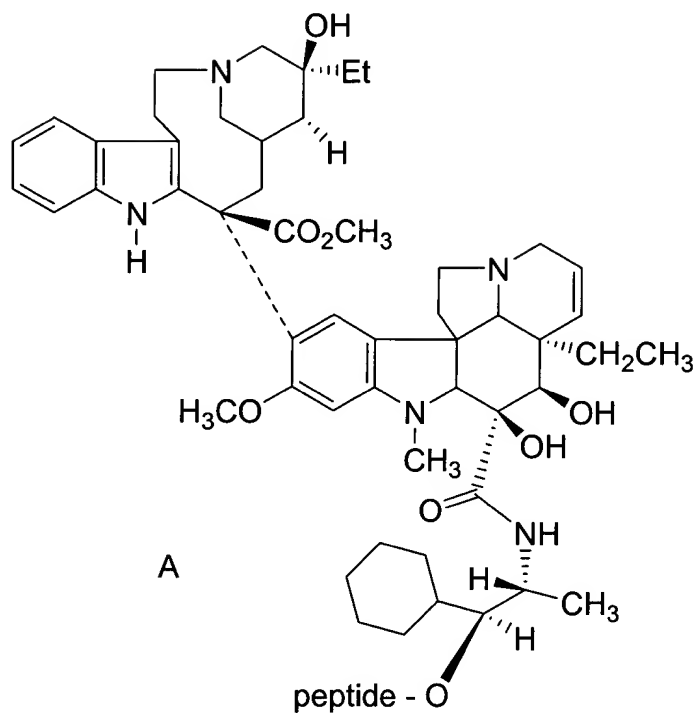
or an optical isomer thereof.

9. (original) The conjugate according to Claim 5 which is selected from:

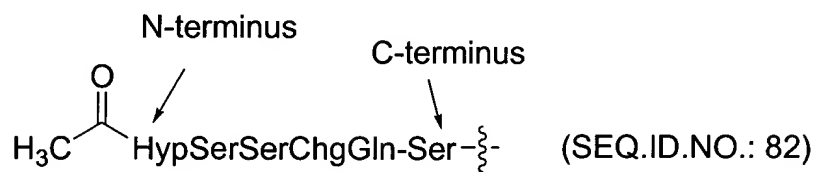
| <u>PEPTIDE-VIN CONJUGATE</u>                               | <u>SEQ.<br/>ID.NO.</u> |
|--|------------------------|
| Ac-(4-trans-L-Hyp)SSChgQ-SPheol-(dAc)-VIN                  | 90                     |
| Ac-4-trans-L-HypSSChgQS-cyclopropylalaninol-(dAc)-VIN      | 91                     |
| Ac-4-trans-L-HypSSChgQS-cyclohexylalaninol-(dAc)-VIN       | 92                     |
| Ac-4-trans-L-HypSSChgQS-valinol-(dAc)-VIN                  | 93                     |
| Ac-4-trans-L-HypSSChgQS-(HCAP)-(dAc)-VIN<br>TFA salt       | 82                     |
| Ac-4-trans-L-HypSSChgQS-O-3(R)pyrrolidine-(HCAP)-(dAc)-VIN | 82                     |
| Ac-4-trans-L-HypSSChgQ-SS-(HCAP)-(dAc)-VIN                 | 83                     |
| N-hydroxyacetyl-AbuSSChgQ-SP-(HCAP)-(dAc)-VIN              | 85                     |
| Ac-SSChgQ-SP-(HCAP)-(dAc)-VIN                              | 86                     |
| Ac-AbuSSChgQ-SP-(HCAP)-(dAc)-VIN                           | 84                     |
| Ac-SChgQ-SP-(HCAP)-(dAc)-VIN                               | 94                     |
| Ac-AbuSChgQ-SP-(HCAP)-(dAc)-VIN                            | 95                     |
| Ac-SChgQSS-Sar-(HCAP)-dAc-VIN                              | 96                     |
| Ac-SChgQS-Abu-(HCAP)-VIN                                   | 97                     |
| Ac-SChgQ-SS(4-trans-L-Hyp)-(HCAP)-dAc-VIN                  | 98                     |
| Ac-SChgQSS(PIP)-(HCAP)-dAc-VIN                             | 99                     |
| Ac-SChgQSS(HCAP)-dAc-VIN                                   | 100                    |
| Ac-SChgQSS-gammaAbu-(HCAP)-dAc-VIN                         | 101                    |
| Ac-4-trans-L-HypSSChgQSP(HCAP)-VIN                         | 102                    |
| Ac-SSChgQ-SSP-(HCAP)-dAc-VIN                               | 103                    |
| Ac-SChgQ-SSP-(HCAP)-VIN                                    | 104                    |
| Ac-AbuSSChgQ-S-(HCAP)-VIN                                  | 105                    |

or a pharmaceutically acceptable salt or optical isomer thereof.

10. (amended) A compound of the formula A ~~which is selected~~  
from:

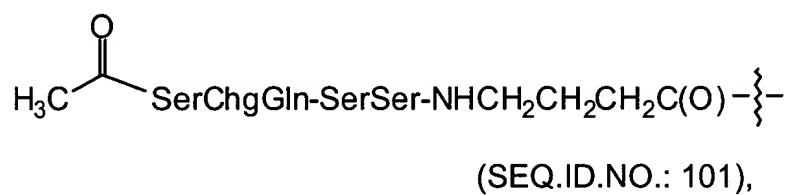


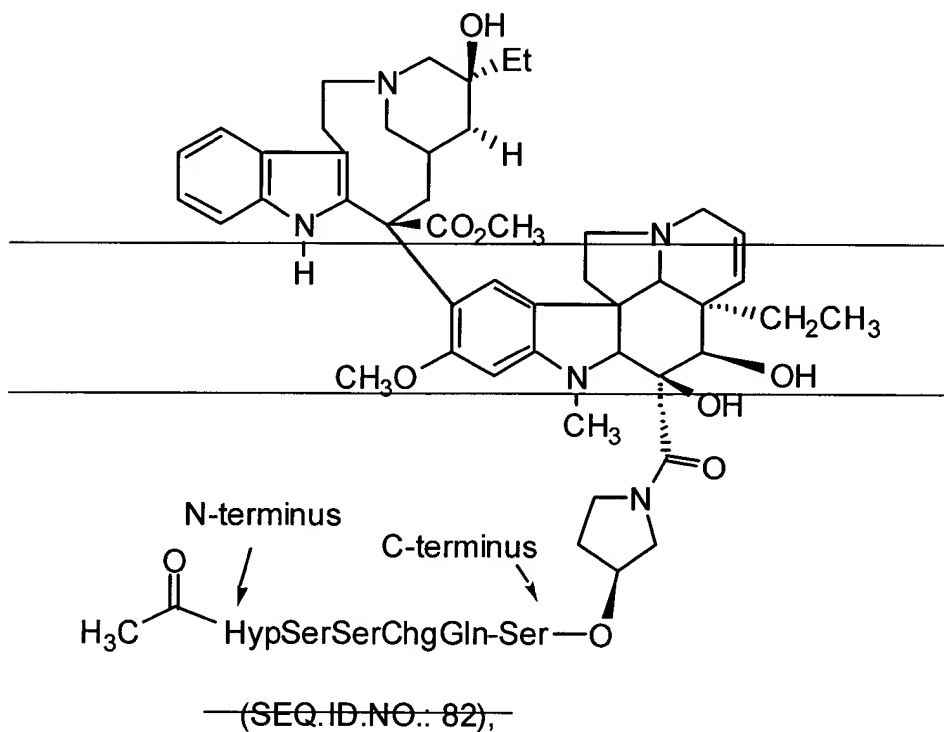
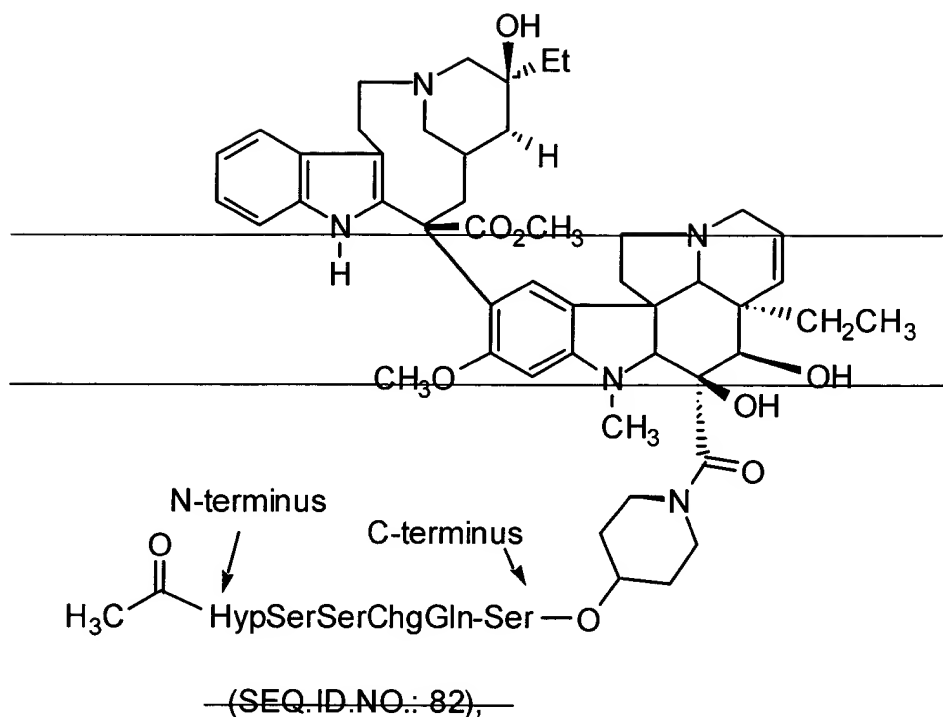
wherein peptide is selected from:





peptide





or the pharmaceutically acceptable salt or optical isomer thereof.

11. (amended) A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a conjugate compound of Claim 1.

12. (amended) A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a conjugate compound of Claim 5.

13. (original) A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 10.

14. (canceled)

15. (canceled)

16. (canceled)

17. (canceled)

18. (amended) A pharmaceutical composition made by combining the conjugate compound of Claim 1 and a pharmaceutically acceptable carrier.

19. (canceled)

20. (canceled)

21. (canceled)

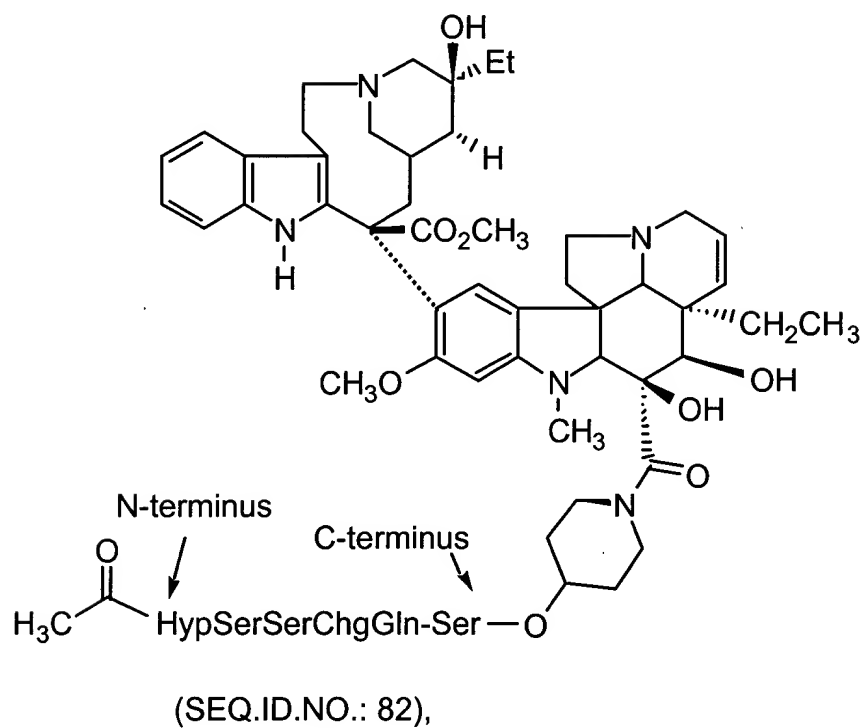
22. (canceled)

23. (canceled)

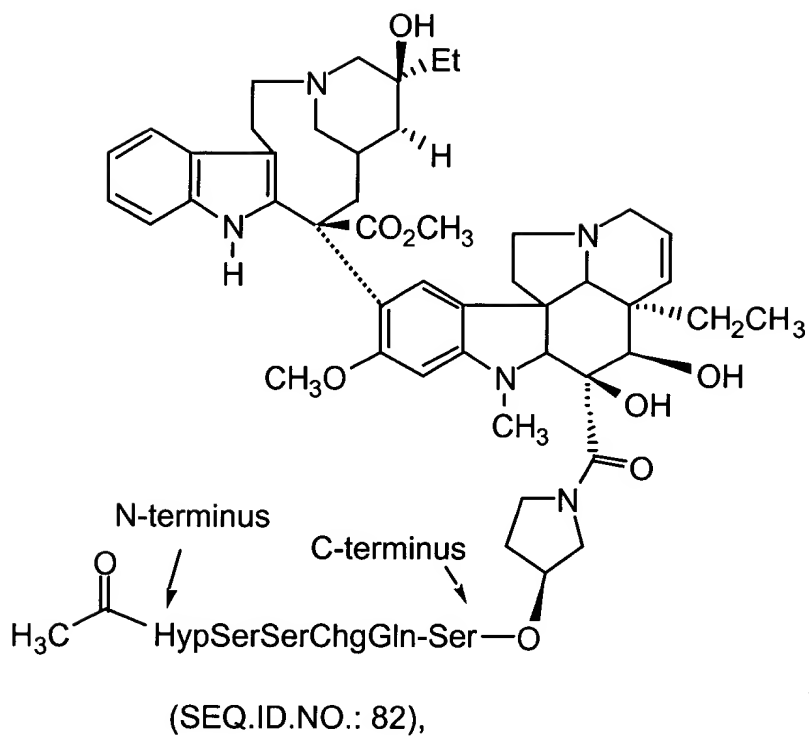
24. (canceled)

25. (canceled)

26. (new) The compound according to Claim 5 selected from:







or the pharmaceutically acceptable salt or optical isomer thereof.